Remarks

Rejections under 35 U.S.C. §112

Claims 1-10, 29-36, and 38-41 stands rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner indicates that the specification is enabling for treating rhinosinusitis or alleviating symptoms of rhinosinusitis with thapsigargin but does not provide enablement for other agents that permit the release of proteins from the endoplasmic reticulum. While Applicants maintain that the original claims are enabled, Applicants have nevertheless amended claim 1 to focus on a particular class of agents that permit the release of proteins from the endoplasmic reticulum (ER), namely agents that decrease or inhibit activity of the ER calcium pump, also known as the ER Ca^{++} ATPase. Support for the amendment is found in original claim 3 and in the specification, e.g., at p. 8, line 24 and p. 9, lines 1-2. Applicants submit that the amended claims are enabled for each of following reasons.

Firstly, when rejecting a claim under the enablement requirement of 35 U.S.C.§112, the examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. *Id.*; and MPEP Section 2164.04. In the instant case, the Examiner has not provided any evidence or technical reasoning that would suggest a lack of enablement.

Instead, the specification clearly establishes the existence of correlations that demonstrate enablement of the claims, and the Examiner has not provided any reasoning to suggest otherwise. As described below, the specification has established that (i) there is a correlation between the ability of an agent to inhibit the ER Ca^{++} ATPase, and the ability of the agent to cause release of proteins from the ER *in vitro* (i.e., in cultured cells); (ii) there is a correlation between the ability of an agent to cause release of proteins from the ER *in vitro* and its ability to do so *in vivo*; and (iii) there is a correlation between the ability of an agent to cause release of proteins from the ER *in vivo* and its use for the treatment of rhinosinusitis or alleviation of symptoms thereof. The

existence of correlations between *in vitro* and/or *in vivo* models and a claimed method is sufficient to establish enablement of the claims, absent evidence to the contrary. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). See MPEP 2164.02.

The specification teaches that agents that inhibit the ER Ca^{++} ATPase cause release of proteins from the ER (p. 9, lines 1-2 and 24-26) and that thapsigargin, DBHQ, and cyclopiazonic acid are three structurally unrelated compounds that inhibit the ER Ca^{++} ATPase (p. 16, lines 20-28 and p. 32, lines 23-28). The specification describes experiments showing that each of these agents causes release of proteins from the ER. Experiments 1-4 (pp. 44-54) and 7 (pp. 55-56), show that treatment with thapsigargin causes increased levels of the CFTR channel in the plasma membrane of CF mutant cells and restores CFTR channel activity. Importantly, *Experiment 3 also shows that treating cells with DBHQ and cyclopiazonic acid also induced delivery of mutant CFTR to the cell surface*. See p. 52, lines 10-14, stating, "we exposed ΣCFBE290⁻ cells to the calcium pump inhibitors DBHQ and cyclopiazonic acid, which are structurally unrelated to thapsigargin (Khan *et al.*, Biochem. 34:14385-14393 (1995); Whitcome *et al.*, Biochem. J. 310:859-868 (1995)). As assayed by immunofluorescence microscopy (data not shown), both compounds were able to recapitulate thapsigargin's capacity to induce ΔF508-CFTR surface delivery." Therefore, it is evident that DBHQ and cyclopiazonic acid share the ability of thapsigargin to cause release of proteins from the ER. It is therefore evident that a correlation exists between the ability of an agent to inhibit the ER Ca^{++} ATPase and the ability of the agent to cause release of proteins from the ER *in vitro*.

The specification also establishes that a correlation exists between the ability of an agent to cause release of proteins from the ER *in vitro* and its ability to do so *in vivo*. In particular, Experiment 8 (pp. 56-60) shows that treatment with thapsigargin reverses a phenotypic defect in CF mutant mice, i.e., it corrects the nasal potential difference in these mice towards more normal values, indicating that the effects of thapsigargin on protein release from the ER observed *in vitro* also occur *in vivo*. The specification therefore clearly establishes that there is a correlation between results showing protein release from the ER *in vitro* and results obtained *in vivo*, i.e., agents that cause release of proteins from the ER *in vitro* such as DBHQ, cyclopiazonic acid, and thapsigargin, will also do so *in vivo*. The Examiner has acknowledged that the specification is enabled for treating rhinosinusitis or alleviating the symptoms of rhinosinusitis with

thapsigargin, i.e., that there is a correlation between the results showing protein release with thapsigargin and the claimed methods.

While it is true that the experiment describing administration of thapsigargin is the only working example containing *in vivo* data, Applicants submit that even if the data was limited to this sole example (i.e., if none of the *in vitro* data discussed above was present), this working example would be sufficient to demonstrate enablement of the claims. As stated in MPEP 2164.02, "The presence of only one working example *should never be the sole reason for rejecting claims as being broader than the enabling disclosure*...To make a valid rejection, one must evaluate all the facts and evidence and *state why one would not expect to be able to extrapolate that one example across the entire scope of the claims*." (emphasis added). Applicants submit that the Examiner has not explained why one would not expect to be able to extrapolate the example of thapsigargin across the entire scope of agents that inhibit the ER Ca^{++} ATPase. The Examiner has also not explained why one would not expect to be able to extrapolate the example of thapsigargin across the entire scope of agents that cause release of proteins from the ER. Therefore, in the absence of such explanations, there is no basis for requiring the claims to be limited to administration of thapsigargin.

Applicants submit that the existence of the correlations mentioned above, clearly establishes that the instant claims are enabled across their full scope. Working examples have been provided for three structurally diverse members of the genus of ER Ca^{++} ATPase inhibitors, all of which cause release of proteins from the ER. Applicants are not required to provide working examples for every member of a claimed genus in order to show enablement. Such a requirement would unduly limit the scope of protection to which Applicants are entitled based on their discovery of the ability of ER Ca^{++} ATPase inhibitors to cause release of proteins from the ER and their inventive methods of treating rhinosinusitis by causing release of proteins from the ER.

Secondly, with respect to the "Wands factors" listed in the office action mailed 5/20/05 as indicating that undue experimentation would be required to practice the claims commensurate with their scope, Applicants submit that (i) the specification does provide experimentation for other agents that permit release of proteins from the ER in addition to thapsigargin, contrary to the statement of the Examiner; (ii) the claims have been narrowed to recite a particular class of

agents, i.e., agents that inhibit the ER Ca^{++} ATPase; (iii) the working examples provide *in vitro* data for DBHQ, cyclopiazonic acid, and thapsigargin showing that these agents cause release of proteins from the ER and establish a correlation between the *in vitro* data and *in vivo* results obtained following administration of thapsigargin to mice.

Thirdly, even if some experimentation is required to practice the claimed methods across their full scope, Applicants submit that such experimentation is merely routine or is described in detail in the specification and is therefore not "undue", in contrast to the Examiner's statement on p. 4 of the instant office action. The Federal Circuit has stated with respect to enablement that, " 'a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Methods for determining whether any particular compound inhibits the ER Ca^{++} ATPase had been well known in the art for some time prior to the filing date of the instant application. See, e.g., Seidler, N.W., "Cyclopiazonic acid is a specific inhibitor of the Ca^{2+}-ATPase of sarcoplasmic reticulum." *J Biol Chem.* 264(30):17816-23 (1989), a copy of which is enclosed herein as Exhibit A, for a representative example. Thus determining whether any particular compound is an ER Ca^{++} ATPase inhibitor is routine. The working examples in the specification provide detailed descriptions of a variety of different methods that one of skill in the art could use to determine whether any particular ER Ca^{++} ATPase inhibitor was indeed effective in causing release of proteins from the ER either *in vitro* or *in vivo*. Therefore, Applicants submit that any experimentation required to carry out the instant claims across their full scope is by no means undue.

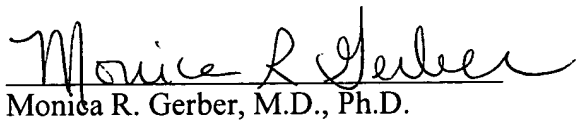
For each of the above reasons, withdrawal of the rejection is respectfully requested.

In light of the foregoing Amendment and Remarks, Applicants respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful or if questions arise regarding the amendment proposed above, please do not hesitate to contact the undersigned at (617) 248-5071.

A petition and check for a three (3) month extension of time are enclosed herein. Please charge any additional fees, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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